Remarks

Claims 1-23 and 25-26 were elected for examination.

In the present Office Action, claims 24-30 have been withdrawn from consideration as being drawn to a non-elected invention. It appears that the Examiner has withdrawn claims 25 and 26 in the present application because they depend from claim 24, which was not elected. The Examiner has further withdrawn claims 8, 18, and 23 from further examination in the present Office Action, asserting that they are also drawn to a non-elected invention.

Species elected for examination in the Response to the Restriction Requirement include:

1) for amino acid sequences: ALA(GLN)n;

2) for antiretroviral drugs: the protease inhibitor, nelfinavir; and

3) for cleavage site: trypsin.

Claims 1-7, 9-17, and 19-22 were examined on the merits.

Claim 7 has been amended herein to correct a typographical error. The comma (",") was inadvertently left out following the term "(Gln)n" and has been added to claim 7 herein. This amendment introduces no new matter and is supported throughout the specification as filed. For example, at page 7, line 11 of the specification as filed it can be seen that there is a comma after the term "$(Gln)_n$", and it is used in the same context as in claim 7.

Response to withdrawal of claims 8, 18, and 23 in the present Office Action

The Examiner did not require restriction of claims 8, 18, and 23 in the Restriction Requirement, and in fact required species elections related to those claims. However, with this new withdrawal of claims by the Examiner, claims comprising other than the elected species of sequence, i.e., the elected type of inhibitor, and the elected species protease cleavage site, will not be Examined in conjunction with one another and it will be more difficult for the Examiner to consider other species if allowable claims are found. Applicants request that the Examiner reconsider the withdrawal and examine claims 8, 18, and 23. Applicants further submit that the arguments presented below regarding rejected claims are also applicable to claims 8, 18, and 23.

Response to objection to minor informalities

The Examiner has objected to the title of the application- "Use of Stable Glutamine Derivatives to Improve Drug Absorption", asserting that titles are limited to 2-7 words

maximum. The Examiner further states that a title must be clearly indicative of the invention and suggests that eliminating the phrase "Use of" from the title would satisfy the assertion. Applicants respectfully point out that, contrary to the assertion of the Examiner, titles are not limited to 2-7 words. In fact, a title is limited to 500 characters, not a specific number of words. MPEP § 606 and 37 CFR 1.72. Moreover, the MPEP further states that the title should be technically accurate and descriptive. Additionally, a title should only be changed if it is not descriptive of the invention, and if changed to do so can actually be longer than the original title. MPEP § 606.01. As the claims under consideration are method claims for the use of a compound, or are claims drawn to compositions comprising said compounds for said use, Applicants respectfully submit that the title is in compliance with MPEP §§ 606 and 606.01 and 37 CFR 1.72 and request that the objection be withdrawn.

Response to rejection of claims 1, 3-7, 9-11, 13-17, and 19 as anticipated by Guerrant et al. (U.S. Pat. No. 5,561,111) under 35 U.S.C. § 102(b)

Examiner asserts that the present claims are drawn to a method of enhancing the absorption of a pharmaceutical agent administered orally to a mammal, the method comprising the steps of administering to the mammal a glutamine-bearing compound (Ala(Gln)n), and the pharmaceutical agent, wherein the mammal is a human having compromised intestinal function.

The Examiner further asserts that Guerrant teaches a method for the treatment of dehydration or nitrogen deficiency-based malnutrition comprising administering to a subject an effective amount of a compound selected from oligopeptides formed from the coupling of one or more amino acids with glutamine, the product of coupling glucose with glutamine, the product of coupling glucose and one or more amino acids with glutamine, or the product from acylating glutamine with a carboxylic acid having from 2 to 6 carbon atoms (citing the abstract). It is the view of the Examiner that this reads on claims 1, 3-5, 11, and 13-15, asserting that glucose can be used as a pharmaceutical as a restorative agent after severe operations or as a nutritive in wasting disease, referring to the British Pharmaceutical Codex. The Examiner further asserts that Guerrant teaches that the glutamine derivatives can be administered either orally or intravenously (citing column 4, lines 24-25) and that this reads on claim 4. The Examiner also asserts that Guerrant teaches Ala-Gln (citing the Example and Fig. 1) and that this reads on claims 6, 7, 9, 10, 16, 17, and 19.

Applicants traverse the rejection for the following reasons.

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, the Guerrant reference must describe each and every element of claims 1, 3-7, 9-11, 13-17, and 19 in order to anticipate these claims under Section 102(b), and this reference does not.

Applicants respectfully submit that Guerrant does not teach, or even contemplate, enhancing absorption of a pharmaceutical agent using glutamine as recited in the present application. Guerrant only teaches methods of delivering glutamine itself, by modifying glutamine for the "treatment of dehydration or nitrogen deficiency-based malnutrition." For example, at column 2, line 66 to column 3, line 2 it is stated, "Accordingly, one object of the invention is to provide new stable glutamine derivatives **capable of delivering glutamine** to the body in oral or intravenous rehydration or nutrition therapy" (emphasis added). The present application teaches and claims using glutamine to enhance absorption of other compounds, not enhancing absorption of glutamine itself as taught by Guerrant. Further evidence for the difference can be found, for example, where Guerrant discusses the use of that invention for "delivering sufficient amounts of glutamine to the patient to obtain effective amounts in the patient's system to treat conditions associated with dehydration or malnutrition" such as at column 3, lines 14-17.

Guerrant does not teach or even contemplate the use of glutamine or glutamine derivates to enhance the absorption of other compounds as taught and claimed in the present application. For example, the present application demonstrates that glutamine and glutamine derivatives enhance absorption of antiretroviral drugs as evidence by increased serum levels of those drugs in patients who are HIV positive (see Example 3, Table 1, and Figures 1-3).

Regarding the Examiner's assertion that glucose is a pharmaceutical agent, it was overlooked by the Examiner that the glucose of Guerrant must be coupled to the glutamine (see abstract) and that the glucose is coupled to the glutamine to form a compound which is less susceptible to degradation (see column 3, lines 42-44). Additionally, the data of Guerrant only

addresses absorption of the glutamine derivatives Ala-Glu and Ala-Gln (see Fig. 1) and shows that Gln alone degrades faster under increasingly acidic conditions (See Fig. 2). Nowhere does Guerrant teach or suggest that a glutamine derivative can enhance the absorption of a pharmaceutical agent. Guerrant does not even contemplate such an occurrence. Furthermore, Guerrant does not even use glucose in any of the experiments and does not enable such a use.

Applicants submit that for the reasons described above, Guerrant does not anticipate claims 1, 3-7, 9-11, 13-17, and 19 and request that the rejection as to these claims be withdrawn.

Response to rejection of claims 1, 11, and 12 as anticipated by Petit (U.S. Pat. No. 6,734,170) under 35 U.S.C. § 102(e)

Examiner asserts that the present claims are drawn to a method of enhancing the absorption of a pharmaceutical agent administered orally to a mammal, the method comprising the steps of administering to the mammal a glutamine-bearing compound and the pharmaceutical agent, wherein the mammal is a human subject who is HIV positive having compromised intestinal function and the administered pharmaceutical agent is an anti-retroviral drug.

Applicants point out that claim 1 does not specifically recite a human subject having compromised intestinal function, but that its dependent claim 11 does. Additionally, only claim 12, which depends from claim 11, specifically recites that the subject is HIV positive and the administered pharmaceutical agent is an antiretroviral drug.

Examiner then asserts that Petit teaches a composition and a method for increasing cellular uptake of bioactive agents, particularly those compounds termed "small molecules" into the cells of mammalian tissue, such as the epithelial cells of the mucosa (citing the Petit abstract). The Examiner further asserts that Petit teaches that the composition is a solution dispersion or suspension comprising an aqueous vehicle and an effective amount of a bioactive compound, in combination with an amount of carbohydrate effective to reduce the absolute solubility of the bioactive agent in the aqueous vehicle, so as to achieve increased transport of the agent into the target cells (citing column 2, lines 35-41). The Examiner also states that Petit teaches treating a variety of disorders (citing column 3, lines 5-8), and asserts that this reads on claim 1 in part. The Examiner then asserts that the bioactive agent of Petit is a molecule exerting a therapeutic or nutritive effect on a mammal following absorption of an effective amount of that molecule (citing column 4, lines 9-12), and that the agents include antiviral drugs and antibiotics

(citing column 4, lines 55-56 and column 5, lines 4-7). The Examiner also states that Petit teaches "enhancement of glutamine absorption to treat patients infected with HIV" (citing column 18). The Examiner then asserts that Petit teaches enhancing glutamine absorption into intestinal mucosa for providing a therapeutic benefit to HIV-infected patients and that the benefit includes enhanced cytokine response (citing column 18, lines 30-36). Lastly, the Examiner asserts that the glutamine/carbohydrate carrier composition can be administered in the form of an enteric-coated tablet, caplet, capsule, or coated bead (citing column 18, lines 37-39). It is the view of the Examiner that this reads on claims 1, 11, and 12.

Applicants traverse the rejections for the reasons described below.

Applicants submit that, as described above, the present application teaches and claims using glutamine derivatives to enhance the absorption of other compounds. Contrary to the assertion of the Examiner, Petit does not anticipate claims 1, 11, and 12 because it does not anticipate each and every element of the claims and in fact teaches the use of carbohydrates to enhance the absorption of compounds such as glutamine.

Applicants point out that the phrase "glutamine/carbohydrate carrier composition", which is included at column 18, lines 37-39 cited by the Examiner, means that glutamine is the "bioactive agent" and that the carbohydrate carrier is what is used to enhance glutamine uptake. For example, the title of the section cited by the Examiner is "Enhancement of Glutamine Absorption . . ." and the section encompasses the use of a carbohydrate carrier to enhance the absorption of glutamine.

The examples and all the data disclosed in Petit demonstrate and teach the use of various carbohydrates to enhance absorption of various compounds such as glutamine. Conversely, the present application teaches and claims the use of glutamine and glutamine derivatives to enhance absorption of pharmaceutical agents. Carbohydrates are the only enhancing agents taught or contemplated in Petit. As cited by the Examiner, Petit taught the use of carbohydrates to reduce the solubility of an active agent such as glutamine in at attempt to achieve increased transport of the active agent (column 2, lines 35-41). Petit did not teach the converse. The carbohydrate carriers taught by Petit include monosaccharides such as glucose, disaccharides such as sucrose, or a combination of the two (column 2, lines 52-54). Everything taught by Petit used a carbohydrate as a carrier to enhance absorption of an agent of interest.

Regarding the assertion by the Examiner that Petit teaches enhancing glutamine absorption to treat HIV (citing column 18) and to enhance cytokine response (citing column 18, lines 30-36), the cited section merely refers to glutamine acting directly on T cells, not to glutamine enhancing absorption of other compounds. In fact, the section again used a carbohydrate as the carrier, not the active agent.

Because the present application teaches and claims the use of glutamine/glutamine derivatives as a means of enhancing absorption of other compounds such as antiretroviral drugs, while Petit teaches the use of a carbohydrate as a means of enhancing absorption of compounds such as glutamine or antiretroviral drugs, Petit cannot anticipate the present claims. Applicants requests that for the reasons described above the rejection of claims 1, 11, and 12 as anticipated by Petit be withdrawn.

Response to rejection of claims 2, 12, and 20-22 under 35 U.S.C. § 103(a) as obvious over Guerrant in view of Petit

The Examiner asserts that the present claims are drawn to a method of enhancing the absorption of a pharmaceutical agent administered orally to a mammal, the method comprising the steps of administering to the mammal a glutamine-bearing compound before the pharmaceutical agent, wherein the mammal is a human subject who is HIV positive having compromised intestinal function and the administered pharmaceutical agent is an anti-retroviral drug, zidovudine.

First, Applicants point out that in the species election the antiretroviral drug elected was nelfinavir, not zidovudine as indicated by the Examiner in section 18 of the Office Action. Applicants will address the rejection as to the species elected.

Examiner asserts that Guerrant's teachings are described above, but that the difference between Guerrant and the present claims is that Guerrant does not teach an HIV positive patient and the administration of an antiretroviral drug.

Examiner then asserts teachings of Petit essentially as described above.

It is the opinion of the Examiner that it would have been obvious to one of ordinary skill in the art to combine the teachings of Guerrant and Petit, alleging that both references teach carbohydrate-glutamine compositions that enhance cellular uptake of bioactive agents in the cells of mammalian tissues (citing Petit, column 4, lines 12-18 and Guerrant, column 2, lines 31-34).

The Examiner then discusses the benefits of glutamine uptake and asserts that it would have motivated one of ordinary skill in the art to combine the teachings since glutamine supplementation can provide benefits, including stimulation of immune cells (citing Petit, column 1, lines 51-53) and that glutamine/carbohydrate can provide a therapeutic benefit to HIV patients (citing Petit, column 18, lines 30-32). It is the view of the Examiner that there would be a reasonable expectation of success, asserting that Petit also teaches that the glutamine/carbohydrate carrier composition can be used to treat HIV and that it further teaches that specific antiviral agents may be potentiated (citing column 4, lines 55-58 and column 5, line 7).

Applicants respectfully submit that the combination of Guerrant and Petit does not render claims 2, 12, and 20-22 *prima facie* obvious under 35 U.S.C. § 103(a), for the following reasons.

The three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

Additionally, MPEP § 2143.01 provides: "The mere fact that references <u>can</u> be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)." However, the TSM test must not be rigidly applied (KSR Intern. Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007)), but to determine whether there is an apparent reason to combine the known elements in the fashion as claimed, the analysis should be made explicit by the Examiner (*Id*).

The determination of obviousness under 35 U.S.C. § 103 is a legal conclusion based on factual evidence. *See Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332, 1336-37 (Fed. Cir. 2005). The legal conclusion, that a claim is obvious within § 103(a), depends on at least four underlying factual issues set forth in *Graham v. John Deere Co. of Kansas City*,

383 U.S. 1, 17, 86 S. Ct. 684, 15 L.Ed.2d 545 (1966): (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) evaluation of any relevant secondary considerations.

The Examiner has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested, by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); MPEP § 2143.03. "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970); MPEP § 2143.03. As part of establishing a *prima facie* case of obviousness, the Examiner's analysis must show that some objective teaching in the prior art or some knowledge generally available to one of ordinary skill in the art would lead an individual to combine the relevant teaching of the references. *Id.* To facilitate review, this analysis should be made explicit. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. ____ (2007) (slip opinion at 14) (citing *In re Kahn*, 441 F. 3d 977, 988 (Fed. Cir. 2006)).

None of these criteria have been met here.

Of course these are guiding principles for analyzing obviousness, but Applicants submit that under any analysis, the cited references do not render the claims obvious for the following reasons.

The arguments and explanations provided above by the Applicants regarding Guerrant and Petit apply with equal force here. As noted above, the particular passages cited by the Examiner were taken out of context relative to their intent, use, and teachings in both Guerrant and Petit.

Contrary to the assertions of the Examiner, nowhere in Guerrant or Petit is it disclosed or suggested that glutamine or derivatives of glutamine can be used to enhance absorption of other compounds or agents as is taught and recited in claims 2, 12, and 20-22 of the present application. As described above, Guerrant teaches methods for enhancing the uptake of glutamine in order to increase the available glutamine in a subject, while Petit teaches using carbohydrates to enhance uptake of glutamine (or other agents) to increase the available glutamine (or other agents0 in a subject. The passage cited by the Examiner in Petit specifically regarding a carbohydrate carrier enhancing the uptake of glutamine refers to the direct effects of

glutamine on T cells and the cytokine response and Petit was applying its carbohydrate carrier technology to enhance the uptake of glutamine (column 18, lines 17-41). Petit did not teach the use of glutamine or glutamine derivatives to enhance the uptake of antiretroviral drugs as suggested by the Examiner.

The present application does not teach or claim enhancement of glutamine absorption itself as a means of treating a disease or disorder as disclosed in Guerrant and Petit, nor does the present application teach or suggest the use of a carbohydrate carrier such as glucose or sucrose to enhance glutamine uptake as taught by Petit. Applicants point out that nowhere in Guerrant or Petit is it taught or suggested that glutamine or a glutamine derivative can be used to enhance the uptake of another compound or pharmaceutical agent such as an antiretroviral compound, such as is recited in claim 12 of the present application and as disclosed in Example 3 of the present application.

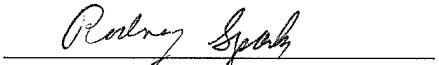
In light of the foregoing arguments, it is clear that the above-identified references do not suggest to, or motivate, one of skill in the art to modify or combine the disclosure of said references to obtain the present invention. Nor would there have been any reasonable expectation of success in such combination since the combination of these references does not teach or suggest all of the claim limitations of claims 2, 12, and 20-22 as required under 35 U.S.C. §103(a). Therefore, Applicants respectfully request that the obviousness rejection be reconsidered and withdrawn.

Conclusion

If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (434) 243-6103.

Respectfully submitted,

Date: January 23, 2008



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